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Ewing's sarcoma of the bone: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Ewing tumors of bone are the second most common primary malignant bone cancer in children and adolescents, but are also seen in adults. The median age at diagnosis is 15 years and there is a male predilection of 1.5/1. Ewing's sarcoma (ES)/peripheral neurectodermal tumors (PNETs) are diagnosed in white Caucasians at an incidence of 3 per million population per year, but are very uncommon in African and Asian populations.

diagnosis

The first symptom is usually pain—often erroneously attributed to trauma. Plain radiographs in two planes, complemented by computed tomography (CT) and/or magnetic resonance imaging (MRI) are indicative of a malignant tumor. Patients with suggestive findings should be referred to a center with particular experience in bone sarcoma before performing a biopsy. The definitive diagnosis is made by biopsy, providing sufficient material for conventional histology and molecular biology (fresh, unfixated material). ES/PNETs are small blue round-cell tumors, PAS- and CD99 (MIC2)-positive. Confirmation of diagnosis by a pathologist with particular expertise in bone tumors is recommended [IV, C]. All ES/PNETs are high-grade tumors. While the degree of neurological differentiation used to be applied to differentiate classical ES from PNET, newer molecular biology studies have shown that all ES/PNETs share a common gene rearrangement involving the EWS gene on chromosome 22. In most cases, a reciprocal translocation t(11;22)(q24;q12) is found, but t(21;22)(q22;q12) and others may also be found.

staging and risk assessment

Before biopsy, the description of the local extent of the tumor requires radiographic and CT/MRI of the entire involved bone, including adjacent joints and soft tissues. For planning of local therapy, the precise involvement of bone, bone marrow and soft tissues including the relationship to critical structures like nerves or vessels, must be specified. A chest CT scan is required to rule out lung or pleural metastases. The assessment for bone and bone marrow metastases is to include ^{99}mTc bone scintigraphy, to detect osseous metastases, and light microscopic examination of bone marrow aspirates and biopsies taken at sites distant from the primary tumor. Positron emission tomography (PET) scanning for bone metastases and PCR techniques to investigate for bone marrow metastases are sensitive imaging methods currently under evaluation. Additional appropriate imaging studies and biopsies should be taken from suspicious sites, as the exact staging of the disease has impact on treatment and outcome [III, B].

About 20% of the patients have ES/PNETs of the pelvic bones, 50% show extremity tumors. ES/PNETs may involve any bone and (less commonly) soft tissues. Twenty to twenty-five percent of the patients are diagnosed with metastatic disease (10% lung, 10% bones, 5% combinations or others).

With surgery or radiotherapy alone, 5-year survival is <10%. With treatment in current multimodality trials including chemotherapy, survival approximates to 60–70% in localized and 20–30% in metastatic disease. Bone metastases confer a poorer outcome than lung/pleura metastases (<20% versus 20–40% 5-year survival) [IIa, B]. Other known prognostic factors are tumor size or volume, serum lactate dehydrogenase (LDH) levels, axial localization or older age (>15 years). Under treatment, poor histological response to preoperative chemotherapy, and incomplete or no surgery for local therapy are further adverse prognostic factors [IIa, B].

treatment plan

As ES/PNETs are rare cancers, and their management is complex, the accepted standard is treatment in specialized centers and in the framework of co-operative trials.

localized disease

Multimodal approaches within clinical trials, employing combination chemotherapy and surgery and/or radiotherapy, have raised 5-year survival rates from <10% to >60%. All

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current trials employ three to six cycles of initial chemotherapy after biopsy, followed by local therapy and another six to ten cycles of chemotherapy usually applied at 3-week intervals. Treatment duration is thus 8–12 months. Agents considered most active include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin and etoposide. Virtually all active protocols are based on four- to six-drug combinations of these substances. The protocols that have proved to be most effective include at least one alkylating agent (ifosfamide or cyclophosphamide) and doxorubicin [Ib, A]. The incorporation of ifosfamide and etoposide into the treatment regimen significantly improved the outcome for patients with non-metastatic ES/PNETs in a randomized trial.

Despite lively debate, complete surgery, where feasible, is regarded as the best modality of local control. Radiotherapy should be applied if complete surgery is impossible, and should be discussed where histological response in the surgical specimen was poor (i.e. >10% viable tumor cells) [IV, C]. In one large series it was found that incomplete surgery followed by radiotherapy was not superior to radiotherapy alone. Radiotherapy is applied at doses of 40–45 Gy for microscopic residues and 50–60 Gy for macroscopic disease [III, B].

metastatic and recurrent disease

Outside specific clinical trials, patients with metastatic disease ought to receive therapy similar to that given for localized disease, with appropriate local treatment of metastases, commonly applied as radiotherapy. Several non-randomized trials have assessed the value of more intensive, time-compressed or high-dose chemotherapy approaches, followed by autologous stem-cell rescue, but evidence of benefit, e.g. resulting from randomized trials, is still lacking [III, B]. Their use may be justifiable in selected patients with isolated lung metastases on an individual basis. In patients with lung metastases, the resection of residual metastases after chemotherapy, and whole lung irradiation may confer a survival advantage [III, B]. Patients with bone or bone marrow metastases and patients with recurrent disease still fare poorly, with 5-year survival rates of ≤20%.

The only prognostic factor identified in relapse seems to be time to relapse: patients relapsing later than 2 years from initial diagnosis have a better outcome [III, B]. Chemotherapy regimens in relapse situations are not standardized and are commonly based on alkylating agents (cyclophosphamide, ifosfamide) in combination with topoisomerase inhibitors (etoposide, topotecan). Doxorubicin therapy is usually no longer feasible due to previously achieved cumulative doses [III, B].

response evaluation

The best radiological method used for local staging should be repeated after palliative or neoadjuvant chemotherapy and after definitive local therapy. MRI may provide the most accurate evaluation of response. In case of neoadjuvant chemotherapy histologic response should be evaluated in the resection specimen. The proportion of viable tumor cells provides prognostic information and may guide the use of further therapy including radiotherapy in localized disease.

follow-up

Most relapses occur in the first 3 years of follow-up; late relapses have rarely been observed even after 15 years or longer. Beside the detection of relapse, long-term sequelae of treatment are the main concern in long-term follow-up. Impaired renal function may be observed early in follow-up, but cardiac or pulmonary damage may become apparent later. Secondary cancers may arise in irradiated sites. Secondary leukemia, particularly acute myeloid leukemia, may rarely be observed independent of previous irradiation as early as 2–5 years after treatment [III, B]. Follow-up intervals should be 2–3 months during the first 3 years, 6 months until 5 years and at least once yearly thereafter. Follow-up is more specifically detailed in concurrent clinical trial manuals, e.g. EURO-E.W.I.NG. 99.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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